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STUDIES ON PYRIMIDINE DERIVATIVES AND RELATED COMPOUNDS. LII.

REACTION OF THIAMINE WITH PHOSPHITES (I)

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Thiamine (B_1) pyrophosphate is recognized as co-carboxylase, B_1 monophosphate and B_1 triphosphate are also well known. However, nothing has yet been reported on the B_1 phosphorous derivatives substituted at other positions of the hydroxyethyl group. In the preceding papers, the authors reported that the reaction of B_1 with aldehydes (1) or amines (2) occurred at the B_1-thiazole (th)-C_2-position, in the different modes of HET type products, via nucleophilic B_1-carbene or pseudo B_1 type intermediate, respectively. Recently, Ramirez et al. (3) reported that the unique acyloxycarbene was held responsible for the formation of the phthalide from phthalic anhydride and triethyl phosphite, and added diethyl phosphite captured the acyloxycarbene to give diethyl phthalide phosphonate. From this fact the authors are interested in the reaction of dialkyl phosphite with B_1. After having been saturated with CO_2, diethyl hydrogenephosphite (III) was added to B_1-Na (I) in toluene or EtOH affording colorless crystals (V), m.p. 133-135°. V was also obtained from the reaction of B_1-chloride (II) with III in the presence of NEt_3 or other suitable bases. V showed analytical data for $C_{16}H_{27}O_4N_4SP$ corresponding to the 1 : 1 adduct of B_1 and diethylhydrogenephosphite. From the UV spectrum [λ_{max}^{EtOH} mμ (ε): 234.5 (9,875), 275 (5,250)] it was estimated that 2-methyl-4-amino-5-pyrimidinyl group might still remain. IR spectrum showed absorption bands at 3390, 3375, 1668 (NH_2), 1252 (P=O), and at 1042 cm^{-1} (P-O-C). NMR spectrum (τ values) showed peaks at 2.00^s (1H, pyrimidine (pm)-C_6-H), 3.99^b (2H, pm-C_4-NH_2), 7.60^s (3H, pm-C_2-CH_3), and at 8.50^s (3H, th-C_4-CH_3) which was extremely higher than that expected as th-C_4-CH_3 signal, in addition, typical signals corresponding to the hydroxyethyl group were deformed and shifted. From the above spectral considerations, it was supported that the cyclization occurred similar to the case of preceding aldehydes or amines to form tetrahydrofuran ring by the reaction of the hydroxyethyl group with th-C_4-C_5-double bond. Accordingly, the structure of V was confirmed to be diethyl 2-{3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-d] thiazole} phosphonate.

Benzoylation of V afforded monobenzoate (VII), m.p. 114°. Physicochemical data of VII [λ_{max}^{EtOH} mμ (ε): 229 (19,900), 273 (6,090); ν_{max}^{Nujol} cm^{-1}: 1675 (C=O); τ in $CDCl_3$: 1.90^{s} (1H, pm-C_6-H), 3.15^{b} (1H, pm-C_4-NH), 7.46^{s} (3H, pm-C_2-CH_3), 8.45^{s} (3H, th-C_4-CH_3)] indicated the structure to be diethyl 2-{3-(2-methyl-4-benzoylaminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-d] thiazole} phosphonate. The fact was provided for the chemical proof that V has a tetrahydrofuran ring in the molecule. V by heating to reflux in EtOH afforded the isomer (VIII), m.p. 160-161° in good yield showing analytical data for $C_{16}H_{27}O_4N_4SP$ corresponding to that of V. From the absorption curve [λ_{max}^{EtOH} mμ (ε): 244 (8,450), 287 (6,250)] it is assumed that the structure of VII may be taking a tricyclic form like dihydrothiochrome cyclizing at the pm-C_4-amino group. IR spectrum of VIII showed bands at 3180, 1610 (NH), 1221 (P=O), and at 1022 (P-O-C) indicating the existence of diethoxyphosphinyl group. NMR spectrum showed peaks at 2.06^{s} (1H, pm-C_6-H), 4.20^{b} (1H, NH), 7.56^{s} (3H, pm-C_2-CH_3), and at 8.50^{s} (3H, th-C_4-CH_3) indicating that the th-C_4-carbon was still saturated. In view of the above facts the structure of VIII was assumed to be diethyl 7-{2,9a-dimethyl-9(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido-[4,5-d] thiazolo[3,4-a]-pyrimidine} phosphonate produced from the result of the recyclization at pm-C_4-amino group with regenerated th-C_4-C_5 double bond following the cleavage of the tetrahydrofuran ring. Benzoylation of VIII with benzoyl chloride in pyridine afforded monobenzoate (X), m.p. 107°, which showed bands at 1717 (C=O), 1612 (NH), and at 1273 (O-C=O) cm^{-1} in the IR spectrum. The data makes clear that the benzoylation may occur in a hydroxyethyl group but not in an amino group. NMR spectral data also shows appropriate signals [τ 2.05^{s} (1H, pm-C_6-H), 4.31^{b} (1H, NH), 7.55^{s} (3H, pm-C_2-CH_3), 8.48 (3H, th-C_4-CH_3), 1.9-2.75^{m} (5H, ph)]. Accordingly, the structure of VIII was confirmed entirely. When aqueous hydrochloric acid solutions of V and VIII were allowed to stand at room temperature B_1-HCl was obtained in a quantitative yield, respectively. Similar reaction was carried out for B_1 with dimethyl phosphite and the results obtained are as follows: VI [m.p. 168-169°; λ_{max}^{EtOH} mμ (ε): 235 (9,975), 275.5 (5,360); ν_{max}^{Nujol} cm^{-1}: 3410, 3285, 1637 (NH_2), 1210 (P=O), 1037 (P-O-C); τ in $CDCl_3$: 2.01^{s} (1H, pm-C_6-H), 4.00^{b} (2H, pm-C_4-NH_2), 7.53^{s} (3H, pm-C_2-CH_3), 8.17^{s} (3H, th-C_4-CH_3)], which was isomerized to give IX [m.p. 173-175°; λ_{max}^{EtOH} mμ (ε): 244 (8,560), 287 (6,370); ν_{max}^{Nujol} cm^{-1}: 3200, 1614 (NH), 1224 (P=O), 1040 (P-O-C); τ in $CDCl_3$: 2.03^{s} (1H, pm-C_6-H), 4.18^{b} (1H, NH), 5.80^{s} (2H, pm-C_5-CH_2-), 7.55^{s} (3H, pm-C_2-CH_3), 8.48^{s} (3H, th-C_4-CH_3)], respectively. The mechanism of this reaction may be considered to proceed in a similar manner as that of

Chart 1

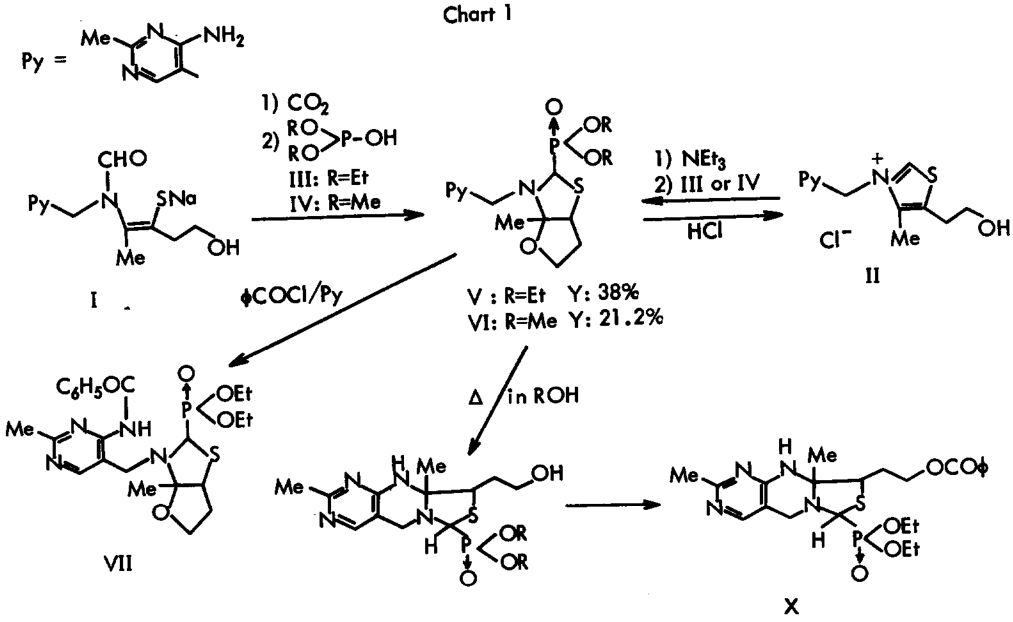
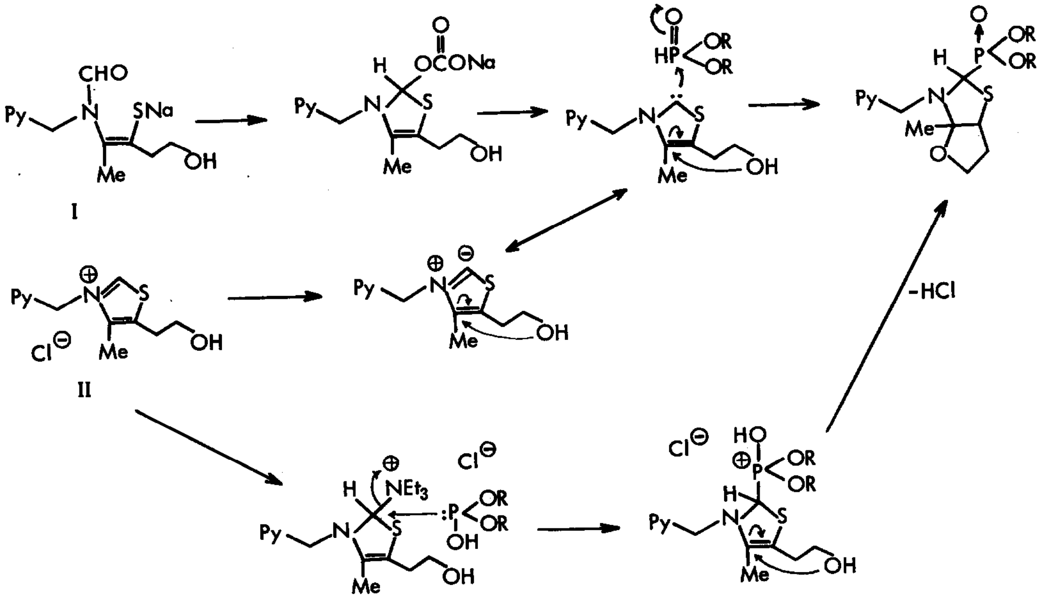


Chart 2



B_1 with aldehydes (Chart 2), however, the more or less concerted reaction mechanism also can not be ruled out although dialkylphosphite has low nucleophilicity (4).

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